PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SPH/CP6211973	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB2004/001225	International filing date *(day/month/year)* 19.03.2004	Priority date *(day/month/year)* 21.03.2003
International Patent Classification (IPC) or both national classification and IPC A61P25/18, A61K31/138, A61K31/48		
Applicant CURIDIUM LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.01.2005	01.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Skjöldebrand, C Telephone No. +49 89 2399-8467

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB2004/001225

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-76 as originally filed

Claims, Numbers

1-19 filed with the demand

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-11
	No:	Claims	1-6, 12-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents, cited in the I.S.R.:

D1: US-B1-6 335 371 (MAEKI-IKOLA OUTI) 1 January 2002 (2002-01-01)

D2: WO 01/96328 A (BANG ANDERSEN BENNY ; FELDING JAKOB (DK); ANDERSEN KIM (DK); KEHLER JA) 20 December 2001 (2001-12-20)

D3: EP-A-0 470 039 (LUNDBECK & CO AS H) 5 February 1992 (1992-02-05)

D4: WO 03/091250 A (WYETH CORP ; RAMAMOORTHY SIVARAMAKRISHNAN P (US)) 6 November 2003 (2003-11-06)

D5: SODHI M S K ET AL: "Epigenetic influences on the serotonin2c (5 - HT2c) receptor in psychiatric disorders." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2003, 2003, pages Abstract No. 317.4 URL-http://sf, XP011822237 & 33RD ANNUAL MEETING OF THE SOCIETY OF NEUROSCIENCE; NEW ORLEANS, LA, USA; NOVEMBER 08-12, 2003

D6: MARCHESE G ET AL: "Different 5-HT2A/2C antagonists impair dopamine re-uptake in the rat brain: role in catalepsy" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, pages Abstract No.-271.13, XP001182407 & 30TH ANNUAL MEETING OF THE SOCIETY OF NEUROSCIENCE; NEW ORLEANS, LA, USA; NOVEMBER 04-09, 2000 ISSN: 0190-5295

D7: WOOD MARTYN D ET AL: "5-HT2C receptor antagonists: Potential in schizophrenia" DRUG DEVELOPMENT RESEARCH, vol. 54, no. 2, October 2001 (2001-10), pages 88-94, XP009032839 ISSN: 0272-4391

D8: MATTEO DI V ET AL: "SB 242 084, A SELECTIVE SEROTONIN2C RECEPTOR ANTAGONIST, INCREASES DOPAMINERGIC TRANSMISSION IN THE MESOLIMBIC SYSTEM" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 38, no. 8, August 1999 (1999-08), pages 1195-1205, XP000985700 ISSN: 0028-3908

D9: BONACCORSO STEFANIA ET AL: "SR46349-B, a 5-HT2A/2C receptor antagonist, potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens" NEUROPSYCHOPHARMACOLOGY, vol. 27, no. 3, September 2002 (2002-09), pages 430-441, XP002288018 ISSN: 0893-133X

D10: KURTZ G ET AL: "Therapy of schizophrenic patients with negative symptoms. Neuroleptic agents of the new generation" PSYCHOPHARMAKOTHERAPIE 1996 GERMANY, vol. 3, no. 2, 1996, pages 57-65, XP009033022 ISSN: 0944-6877

D11: MELTZER HERBERT Y: "The role of serotonin in antipsychotic drug action" NEUROPSYCHOPHARMACOLOGY, vol. 21, no. 2 SUPPL., August 1999 (1999-08), pages 106S-115S, XP002288019 ISSN: 0893-133X

D12: SCHERER J ET AL: "Effect of a combination of flupentixol and nefazodone on negative, positive, and depressive symptoms in schizophrenic patients. Six case reports" PSYCHOPHARMAKOTHERAPIE 2000 GERMANY, vol. 7, no. 2, 2000, pages 82-86, XP009033549 ISSN: 0944-6877

D13: RIEDEL M ET AL: "Ziprasidone: A new atypical antipsychotic - Results from clinical trials" PSYCHOPHARMAKOTHERAPIE 2002 GERMANY, vol. 9, no. 3, 2002, pages 85-94, XP009033548

ISSN: 0944-6877
D14: NISWENDER COLLEEN M ET AL: "RNA editing of the human serotonin 5-HT2C receptor: Alterations in suicide and implications for serotonergic pharmacotherapy" NEUROPSYCHOPHARMACOLOGY, vol. 24, no. 5, May 2001 (2001-05), pages 478-491, XP002288022 ISSN: 0893-133X

Please refer to the pages, lines etc. of the cited documents as indicated in the International Preliminary Search Report.

D1 (US6335371) describes deramciclane ((IR, 2S, 4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1, 7, 7-trimethyl-bicyclo [2.2. 1] heptane) in the treatment of mild cognitive impairment, also in conjunction w. schizophrenia.

D2 (WO0196328) discloses 5-HT2C receptor antagonists against the negative symptoms and cognitive deficits of schizophrenia.

D3 (EP0470039) describe 3-arylindole or 3-arylindazole derivatives, including lu-26042, as selective 5-HT2 ligands. It is compared with ritanserin and ICI-169369 in tests . Such 5-HT2 antagonist are allegedly active against e.g. the negative symptoms of schizophrenia.

Marchese et al. (D6) demonstrated that ritanserin and 5-HT2C antagonist RS-102221 impair dopamine re-uptake in the rat brain. It is further said that this may have a clinical significance in explaining their known effects on extrapyramidal and negative symptoms in schizophrenic patients.

D7 (Wood et al.) suggest the use of 5-HT2C receptor antagonists in the treatment of the negative symptoms of schizophrenia.

D8 (Di Matteo et al.) teaches that the selective 5-HT2C receptor antagonist SB-242084 is effective against depression and the negative symptoms of schizophrenia.

In D9 (Bonaccorso et al.), it is suggested that mixed 5-HT2A/2C antagonism (SR46349-B) may be more advantageous than selective 5-HT2A antagonism as an adjunct to D2 antagonists to improve cognition and negative symptoms in schizophrenia.

D10 (Kurtz et al.) discloses eltoprazine in the therapy of schizophrenic patients with negative symptoms.

The effects of flupentixol and nefazodone on negative and depressive symptoms in schizophrenic patients is known from D12 (Scherer et al.).

From D13, Ziprasidone is known for treating negative symptoms schizophrenia.

Novelty - Article 33(2) PCT

It should be emphasized that the fact that a substance works under the guise of another mechanism or that it turns positive in a test-method does not per se confer novelty in a medical use claim. The subject-matter of independent claim 6 is therefore not novel in view of e.g. Matteo et al.

None of the above cited documents disclose the substances as claimed in the treatment of refractory schizophrenia, suicidality or mild cognitive impairment. The subject-matter of independent claim 7 is novel.

Novelty for the subject-matter of independent claim 1 is cannot be recognised due to a lack of clarity (cf. below). In view of the receptors listed in claim 2, it appears however obvious that the value of Y is $\geq$ 1,80 for any selective 5-HT2C antagonist, as each of the ratios X/A resp. X/B logically should exceed 1 due to the selectivity. The formula in claim 1 is just an alternative way of expressing selective 5-HT2C antagonist.

In a product/composition claim, the intended therapeutic use is not a novelty establishing feature. The subject-matter of independent claim 17 is not novel in view of e.g. Scherer et al.

Inventive Step - Article 33(3) PCT

For independent claim 7, an inventive step cannot be acknowledged due to the lack of support and disclosure (cf. discussion below). Could the Applicant demonstrate that some of the subject-matter of the other dependent claims was to be novel, an inventive step could not be recognised for the same reason.

Industrial Applicability - Article 33(4) PCT

For the assessment of the present claims 6-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for

example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

Clarity and support in the description - Article 6 PCT

Disclosure of the Invention - Article 5 PCT

The method in claim 1, includes "assessing the affinity of the compound at least two other major sites of said compound interaction". It is not clear what receptors said "other major sites of said compound interaction" might include. Therefore, the skilled man does not know what compounds could come into question. Moreover, in view of the relatively few receptors mentioned in the description, said term "other major sites of said compound interaction" is not supported over its whole breadth.

Moreover, there appears to be no substantiated evidence showing that 5-HT2C receptor antagonists fulfilling said test-criteria really have the claimed therapeutic effect. The disclaimers relating to some 5-HT2C receptor antagonists, Clozapine etc., has obviously been done in order to establish novelty over the prior art. The claimed therapeutic activity appears however to be based on assumptions derived from the known therapeutic effect of such disclaimed substances. The current set of claims is speculative and lacks substantiated support in the description.

CLAIMS

1. A method for determining the suitability of a candidate compound for use in the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment which comprises:

a) assessing the affinity of the compound at the 5-HT2C receptor;

b) assessing the affinity of the compound at at least two other major sites of said compound interaction;

c) applying the assessed affinities to the following formula:

$$\frac{X}{A} + \frac{X}{B} = Y$$

[wherein: X is the affinity of a compound for interaction at the 5-HT2C receptor and A and B are the average affinity values of a compound for interaction at two major sites other than the 5-HT2C receptor];

and selecting compounds in which $Y \geq 1.80$ as suitable compounds for the treatment of cognitive dysfunction in and/or negative symptoms of schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment, provided that:

(a) for the treatment of cognitive dysfunction in and/or negative symptoms of schizophrenia or refractory schizophrenia, the compound selected is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;

(b) for the indications cognitive dysfunction in schizophrenia or mild cognitive impairment, the 5-HT2C receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-

bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and
(c) for the treatment of schizophrenic suicidality, the compound selected is other than clozapine.

2. The method of claim 1 in which A and B are different and are independently selected from the group consisting of the 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, 5-HT_6, 5-HT_7, D_1, D_2-S, D_2-L, D_3, D_4, D_5 M_1, M_2, M_3, M_4, M_5, mACh, α_1, α_2, H_1 or sigma receptors.

3. The method of claim 2 in which A is the value for affinity at the 5-HT2A receptor.

4. The method of claim 2 in which B is the value for affinity at the D2 receptor.

5. The method of claim 1 in which the compound selected has $Y \geq 2.00$.

6. The use of a compound having a relative 5-HT2C affinity of ≥ 1.80, wherein the relative 5HT2C affinity is determined according to the method of any one of claims 1 to 5, in the manufacture of a medicament for the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment, with the proviso that:
(a) for the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia or refractory schizophrenia, the compound is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;
(b) for the indications cognitive dysfunction in schizophrenia or mild cognitive impairment, the 5-HT2C receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-

(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and

(c) for the treatment of schizophrenic suicidality, the compound is other than clozapine.

7. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of refractory schizophrenia, suicidality or mild cognitive impairment, with the proviso that:

(a) for the treatment of refractory schizophrenia, the 5-HT2C receptor antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;

(b) for mild cognitive impairment, the 5-HT2C receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and

(c) for the treatment of schizophrenic suicidality, the 5-HT2C receptor antagonist is other than clozapine.

8. The use according to claim 6 or 7 for the treatment of refractory schizophrenia, with the proviso that the antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.

9. The use according to claim 6 or 7 for the treatment of suicidality, with the proviso that, when the suicidality is in a schizophrenic patient, the 5-HT2C receptor antagonist is other than clozapine.

10. The use of claim 9, wherein the suicidality is in a schizophrenic patient.

11. The use of claim 6 or 7 for the treatment of mild cognitive impairment with the proviso that the antagonist is other than deramciclane or N-desmethylderamciclane.

12. The use of any one of claims 6 to 11 wherein the 5-HT2C receptor antagonist is as described in one of WO 97/16429, WO 97/44334, US 05010078, EP 161,218, EP 401,707, EP 526,434, DE 02834114, EP 210,893, US 03580916, US 05043341, EP 620,222, EP 208,235, EP 437,790, DE 02614406, US 04338317, EP 271,013, EP 110,435, EP 398,326, WO 92/05170, WO 95/01976, WO 96/23783, WO 98/04289, WO 97/48700, WO 00/48602, WO 00/26186, WO 99/58490, WO 99/52517, WO 99/51237, WO 99/46245, WO 99/43319, WO 99/33841, WO 99/33840, WO 99/25356, WO 99/09017, WO 99/03833, WO 99/00119, WO 98/56367, WO 98/52943, WO 98/50358, WO 98/50346, WO 98/50343, WO 98/41527, WO 98/38165, WO 98/30561, WO 98/30546, WO 98/24785, WO 98/21958, WO 98/04261, WO 97/48699, WO 97/41858, WO 97/39001, WO 97/37989, WO 97/20845, WO 97/12880, WO 97/08167, WO 97/06155, WO 97/00872, WO 96/39382, WO 96/30366, WO 96/24351, WO 96/23769, WO 96/18629, WO 96/14320, WO 96/11930, WO 96/11929, WO 96/02537, WO 95/29177, WO 95/25731, WO 95/24194, WO 95/21844, WO 95/18117, WO 95/12591, WO9 94/22871, WO 94/18958, WO 94/18182, WO 94/18170, WO 94/14801, WO 94/04533, WO 94/02462, WO 93/18028, WO 93/18026, WO 93/16081, WO 93/16051, WO 93/14758, WO 93/12790, WO 92/15302, WO 92/10192, WO 91/18602, WO 01/68585, WO 01/68067, WO 01/52855, WO 01/38329, WO 01/26621, WO 01/25229, WO 01/19371, WO 00/76984, WO 00/68181, WO 00/63185, WO 00/62782, WO 00/61129, WO 00/61128, WO 00/37068, WO 00/06165, US 06143325, US 05854248, US 05739336, US 05693645, US 05674875, US 05498618, US 05371093, US 05266571, US

05116852, US 05106855, US 05030656, US 05013735, US 04985352, US 04914107, US 04914100, US 04906639, US 04902691, US 04891376, US 04847261, JP 13220375, JP 12204040, JP 11171865, JP 11080155, JP 10316634, JP 10077271, JP 09040646, JP 08053416, JP 08040999, JP 07228573, JP 07179337, JO 00158067, GB 02303303, GB 02301774, EP 01118610, EP 1070716, EP 01052245, EP 01000944, EP 00905136, EP 00797995, EP 00797994, EP 00769297, EP 00749971, EP 00749967, EP 00718299, EP 00700905, EP 00686393, EP 00682015, EP 0661266, EP 00657426, EP 006554440, EP 00613898, EP 00596449, EP 00559569, EP 00545120, EP 00522226, EP 00511074, EP 00511073, EP 00493687, EP 00484988, EP 00465398, EP 00452074, EP 00389352, EP 00388081, EP 00384228, EP 00379308, EP 00378468, EP 00375297, EP 00374042, EP 00373998, EP 00363963, EP 00354030, EP 00337136, EP 00332528, EP 00320983, EP 00218433 and EP 00145494.

13. The use of any one of claims 6 to 11 in which the 5-HT2C receptor antagonist is AHR-16303B (AH Robins Co. Inc), AP-792 and AT-1015 (Ajinomoto Co. Inc.), BMS-181102 (Bristol Myers Squibb), CV-5197 (Takeda Chemical Industries Ltd), dotarizine (Ferrer Internacional SA), E-2101 (Eisai Co Ltd), eltoprazine (Solvay SA), emopamil (Knoll AG), HT-90B (Chugai Pharmaceutical Co Ltd), ICI-169369 and ICI-170809 (Zeneca Group plc), LU-26042 and LU-29066 (H Lundbeck A/S), NPC-18166 (Scios Inc), Org-38457 (NV Organon), pelanserin (Cinvestav), perbufylline (Siegfried Group), SB-206553 and SB-242084 (SmithKline Beecham), SR-46615A (Sanofi Recherche SA), SUN-9221 (Suntory Ltd) tropoxin (Russian Academy Medical Science) or YM-992 (Yamanouchi Pharmaceutical Co Ltd).

14. The use of any one of claims 6 to 11 in which the 5-HT2C receptor antagonist is Ro-60-0759, RS-102221, SDZ-SER-082,

ICI-169369, deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A or LU-26042.

15. The use of claim 14 in which the 5-HT2C receptor antagonist is deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A or LU-26042.

16. The use of any one of claims 9 to 11 wherein the 5-HT2C receptor antagonist is ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.

17. Products containing a 5-HT2C receptor antagonist and a typical anti-psychotic as a combined preparation for simultaneous, separate or sequential use in schizophrenia or suicidality therapy or the treatment of mild cognitive impairment.

18. A product according to claim 17 in which the 5-HT2C receptor antagonist is identified according to the method of any one of claims 1 to 6.

19. A product according to claim 17 in which the 5-HT2C receptor antagonist is as defined in any one of claims 12 to 16.